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Synthesis of 5-Hydroxymethyl-8-methyl-3-(3-aryl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones and Their Esters

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Abstract: New 5-hydroxymethyl-8-methyl-3-(3-aryl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano-[2,3-c]pyridin-2-ones and their esters were synthesized. The structure of obtained compounds was determined through a complete ^{1}H NMR analysis.

Keywords: 5-Hydroxymethyl-8-methyl-3-(3-aryl-[1,2,4]oxadiazol-5-yl)-2H-pyrano-[2,3-*c*]pyridin-2-ones, [1,2,4]oxadiazoles

Substances that contain a fragment of disubstituted [1,2,4]oxadiazoles are commonly used in drug discovery research as an important bioisostere for esters and amides to improve pharmacokinetic properties of drug candidates.[1]

Oxadiazoles have been the subject of investigation in a number of different therapeutic areas, usually as an alternative for ester or amide functionalities. [1,2,4]Oxadiazoles have been proposed as muscarinic receptor agonist,[2,3] benzodiazepine receptor agonist,[4] histamine H3 receptor antagonist,[5] and antiviral compound.[6] Usually the examples described have been primarily limited by simple alkyl and aryl derivatives.

Nowadays, the group of compounds that include [1,2,4]oxadiazole and coumarine cycles in the same molecule has been successfully synthesized. Thus, the synthetic procedure of 3-(coumarin-4-yl)-[1,2,4]oxadiazoles[7–9] **I**, 5-(coumarin-4-yl)-[1,2,4]oxadiazoles[10] **II**, and

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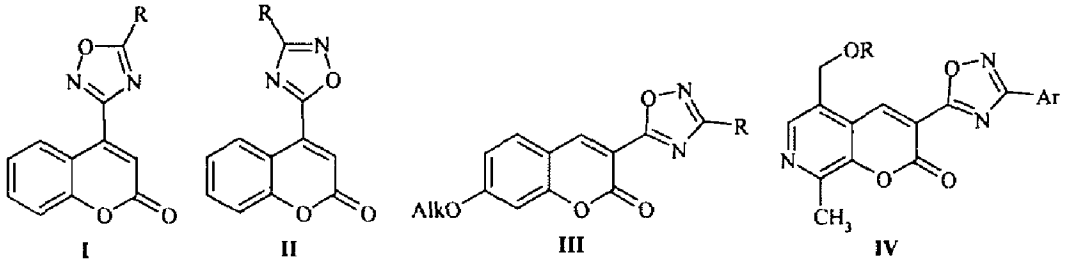
5-(coumarin-3-yl)-[1,2,4]oxadiazoles[11–13] **III** were described. For the structures of **I–III** types, the antioxidant, anti-inflammatory, and anticancer activities were revealed, and the inhibition activity for some proteolytic enzymes was studied.



Azaanalogs of coumarines of type **IV** are novel and have not been synthesized before. However, taking into account the idea of bioisosterism, these compounds should have considerable pharmacological potential.

Earlier, the reaction of pyridoxal hydrochloride with methyleneactive nitriles in an alkaline water media in the presence of the phase-transfer catalyst (cetylmethylammonium bromide) was described by Brufola et al.[14] Only the 2*H*-pyrano[2,3-*c*]pyridines with 2-pyridyl, 2-thienyl or 2-benzothiazolyl heterocyclic moieties in position 3 were successfully obtained by the authors.

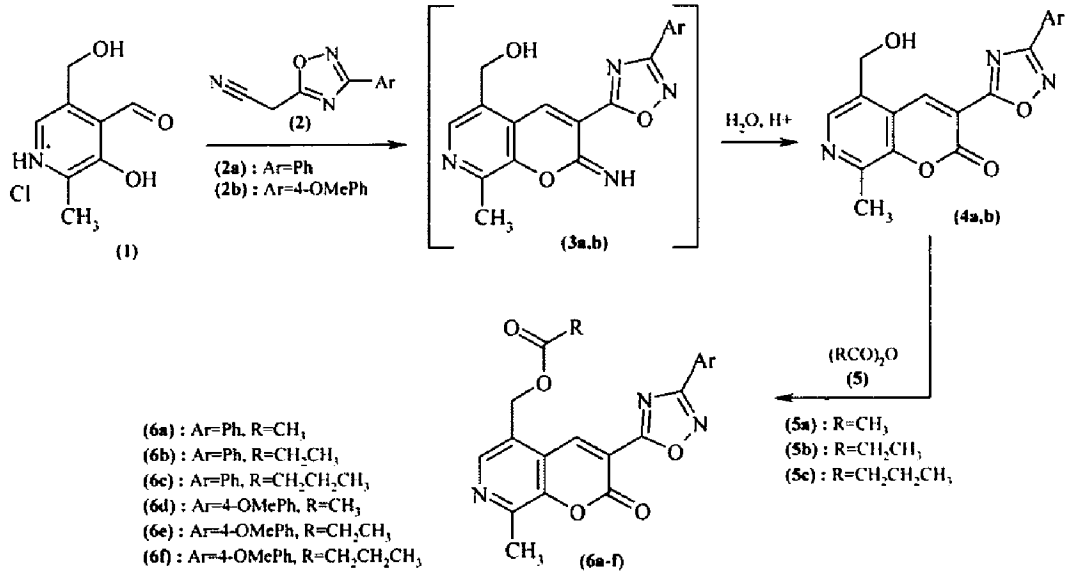
Continuing the investigations in the synthesis of 3-heterylcoumarines[15–18] and their 7-azaanalogs,[19,20] this research work is devoted to preparation of 5-hydroxymethyl-8-methyl-3-(3-aryl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones and their esters.

For synthesis of required compounds, the Knoevenagel condensation of pyridoxal hydrochloride (**1**) with 3-aryl-[1,2,4]oxadiazol-5-yl-acetonitriles (**2a,b**) was developed. The interaction of initial reactants was conducted in homogeneous media in methanol at 45–50 °C in presence of piperidine excess (Scheme 1).

3-Aryl-[1,2,4]oxadiazol-5-yl-acetonitriles (**2a,b**) were obtained by the reaction of corresponding arylamidoximes with 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanonitrile in 1,4-dioxane.

Thin-layer chromatography (TLC) showed that along with formation of 2-imino-2*H*-pyrano[2,3-*c*]pyridines (**3a,b**), their partial hydrolysis takes place, and admixture 2-oxoanalogs (**4a,b**) were identified. For obtaining pure substances (**4**), we conducted the hydrolysis of the products of the reaction in an aqueous–alcoholic media without isolation of the intermediates (**3**).

The ^{1}H NMR spectra of obtained compounds (**4a,b**) contain singlet signals at 8.40–8.42 ppm and 9.07–9.11 ppm, which are caused by the protons H-6 and H-4 in the structure of 2*H*-pyrano[2,3-*c*]pyridine and



Scheme 1.

signals of methyl (singlet at 2.60 ppm) and hydroxymethyl (doublet at 4.80 ppm and triplet at 5.67–5.69 ppm) substitutes. All the spectra of compounds (**4**) also contain signals of aromatics cycle.

The treatment of compounds **4a,b** with anhydride of carbonic acids in boiling glacial acetic acid leads to the corresponding *O*-acylation products (**6a–f**). Isolated yields of **6** were generally high and ranged from 79 to 92%.

In the ^{1}H NMR spectra of *O*-acylderivatives (**6a–f**), the signal of the proton of the hydroxyl group disappears, the multiplicity of H-signals of methylene fragment changes; the H-signals of corresponding acylsubstituents can be observed.

Thus, as a result, a facile approach to 5-hydroxymethyl-8-methyl-3-(3-aryl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones and their esters as potential pharmaceutical agents has been developed.

EXPERIMENTAL

Melting points were measured with a Buchi B-520 melting-point apparatus and were not corrected. IR spectra were recorded on Specord M80 spectrometers in KBr. ^{1}H NMR spectra were recorded on Varian Gemini-300 spectrometers in DMSO-d_6 using TMS as an internal standard. Chemical shifts were expressed in δ (ppm) relative to TMS as internal standard and coupling constants (J) in hertz. Mass spectral analyses were obtained on a PE Sciex API 150EX mass spectrometer. Elemental analysis were within +0.4% of the theoretical value.

Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). The solvent system for the TLC method is ethyl acetate–toluene (1:1 or 1:2).

Arylamidoximes (N-hydroxyamidine of arylcarboxylic acids) were prepared using a previously described approach.[21]

General Procedure for Synthesis of 3-Aryl-[1,2,4]oxadiazol-5-yl-acetonitriles (2a,b)

The mixture of corresponding of arylamidoxime (20 mmol) and 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanonitrile (20 mmol, 3.26 g) in 1,4-dioxane (20 mL) was heated at reflux and stirred for 5 h. The reaction mixture was cooled and poured out in ice-cold water (100 mL). The product of the reaction formed in unctuous consistency and precipitated in a few hours. For purification, flash chromatography was used.

3-Phenyl-[1,2,4]oxadiazol-5-yl-acetonitrile (2a): Yield 79%, mp: 77 °C.
3-(4-Methoxyphenyl)-[1,2,4]oxadiazol-5-yl-acetonitrile (2b): Yield 85%, mp: 69 °C.

General Procedure for Synthesis of 5-Hydroxymethyl-8-methyl-3-(3-aryl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones (4a,b)

The pyridoxal hydrochloride **(1)** (5 mmol, 1.0 g) of was dissolved at 45–50 °C in methanol (50 mL). Piperidine (0.4 g) was added to obtained solution, and 3-aryl-[1,2,4]oxadiazol-5-yl-acetonitriles **(2)** (5.5 mol) were added after 5 min. The resulting mixture was standing for 15 min and then cooled. The formed precipitate was filtered out and dissolved in 50 mL of methanol with 10 mL of diluted HCl (1:10). The resulting mixture was refluxed at 3 h and then cooled. The formed precipitate was filtered out, washed with water (3 × 50 mL), and recrystallized from methanol.

5-Hydroxymethyl-8-methyl-3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (4a): Yield 72%, mp: 235–236 °C; IR, ν, cm^{-1}: 3460, 3308 (OH), 1752 (CO), 1624 (CN), 1600, 1444, 1352; ^1H NMR, δ, ppm: 2.60 (s, 3H, CH_3), 4.80 (d, $J = 6.8$ Hz, 2H, $-CH_2-$), 5.69 (t, $J = 4.9$ Hz, 1H, OH), 7.59 (m, 3H), 8.07 (d, $J = 5.0$ Hz, 2H, H-2′,6′), 8.42 (s, 1H, H-6), 9.11 (s, 1H, H-4). Anal. Calcd. for $C_{18}H_{13}N_3O_4$: C, 64.48; H, 3.91; N, 12.53. Found: C, 64.49; H, 3.90; N, 12.53.

5-Hydroxymethyl-8-methyl-3-[3-(4-methoxyphenyl)-[1,2,4]oxadiazol-5-yl]-2*H*-pyrano-[2,3-*c*]pyridin-2-one (4b): Yield 81%, mp.: 265–267 °C; IR, ν, cm^{-1}: 3332, 3012 (OH), 2396, 2088, 1768 (CO), 1612, 1476, 1428,

1264; ^{1}H NMR, δ, ppm: 2.60 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.80 (d, $J = 5.9$ Hz, 2H, $-CH_2-$), 5.67 (t, $J = 4.7$ Hz, 1H, OH), 7.11 (d, $J = 10.7$ Hz, 2H, H-2′,6′), 8.00 (d, $J = 10.7$ Hz, 2H, H-3′,5′), 8.40 (s, 1H, H-6), 9.07 (s, 1H, H-4). Anal. Calcd. for $C_{19}H_{15}N_3O_5$: C, 62.46; H, 4.14; N, 11.50. Found: C, 64.48; H, 4.14; N, 11.50.

General Procedure for Acylation of 5-hydroxymethyl-8-methyl-3-(3-aryl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones

Compound **4a,b** (2 mmol) was dissolved at 40 °C in a mixture of glacial acetic acid (10 mL) and corresponding anhydride (**5a–c**) (10 mL). The reaction mixture was heated at reflux for 30 min and then cooled to rt. Ice-cold water (50 mL) was added, and the formed precipitate was filtered out and recrystallized from a mixture of ethanol and dimethylformamide to afford the corresponding ether (**6a–f**) as a crystalline solid.

Acetic acid 8-methyl-2-oxo-3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano[2,3-*c*]pyridin-5-ylmethyl ester (6a): Yield 86%, mp: 200–201 °C; IR, ν, cm^{-1}: 1756 (CO), 1744 (CO), 1628 (CN), 1596, 1448, 1244; ^{1}H NMR, δ, ppm: 2.02 (s, 3H, $COCH_3$), 2.60 (s, 3H, CH_3), 5.48 (s, 2H, $-CH_2-$), 7.60 (s, 3H), 8.09 (d, $J = 4.8$ Hz, 2H, H-2′,6′), 8.52 (s, 1H, H-6), 9.05 (s, 1H, H-4). Anal. Calcd. for $C_{20}H_{15}N_3O_5$: C, 63.66; H, 4.01, N; 11.14. Found: C, 63.66; H, 4.00; N, 11.13.

Propyonic acid 8-methyl-2-oxo-3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano[2,3-*c*]pyridin-5-ylmethyl ester (6b): Yield 91%, mp: 162–163 °C; ^{1}H NMR, δ, ppm: 1.00 (t, $J = 9.4$ Hz, 3H, CH_2CH_3), 2.32 (q, $J = 8.5$ Hz, 2H, CH_2CH_3), 2.60 (s, 3H, CH_3), 5.48 (s, 2H, $-CH_2-$), 7.60 (m, 3H), 8.08 (dd, $J = 6.4$ Hz, $J = 3.5$ Hz, 2H, H-2′,6′), 8.50 (s, 1H, H-6), 9.05 (s, 1H, H-4). Anal. Calcd. for $C_{21}H_{17}N_3O_5$: C, 64.45; H, 4.38; N, 10.74. Found: C, 64.45; H, 4.40; N, 10.75.

Butyric acid 8-methyl-2-oxo-3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-2*H*-pyrano[2,3-*c*]pyridin-5-ylmethyl ester (6c): Yield 79%, mp: 145–146 °C; ^{1}H NMR, δ, ppm: 0.83 (t, $J = 9.6$ Hz, 3H, $CH_2CH_2CH_3$), 1.55 (qv, $J = 8.7$ Hz, 2H, $CH_2CH_2CH_3$), 2.30 (t, $J = 8.3$ Hz, 2H, $CH_2CH_2CH_3$), 2.60 (s, 3H, CH_3), 5.49 (s, 2H, -CH_2-), 7.61 (m, 3H), 8.08 (m, 2H, H-2′,6′), 8.52 (s, 1H, H-6), 9.05 (s, 1H, H-4). Anal. Calcd. for $C_{22}H_{19}N_3O_5$: C, 65.18; H, 4.72, N; 10.36, Found: C, 65.21; H, 4.71; N, 10.34.

Acetic acid 8-methyl-2-oxo-3-{3-(4-methoxyphenyl)-[1,2,4]oxadiazol-5-yl}-2*H*-pyrano[2,3-*c*]pyridin-5-ylmethyl ester (6d): Yield 92%, mp: 180–181 °C; ^{1}H NMR, δ, ppm: 2.02 (s, 3H, $COCH_3$), 2.60 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.46 (s, 2H, $-CH_2-$), 7.12 (d, $J = 9.4$ Hz, 2H, H-2′,6′), 8.02 (d, $J = 9.9$ Hz, 2H, H-3′,5′), 8.50 (s, 1H, H-6), 9.03 (s, 1H,

H-4). Anal. Calcd. for $C_{21}H_{17}N_3O_6$: C, 61.92; H, 4.21; N, 10.31. Found: C, 61.91; H, 4.21; N, 10.30.

Propyonic acid 8-methyl-2-oxo-3-{3-(4-methoxyphenyl)-[1,2,4]oxadiazol-5-yl}-2*H*-pyrano[2,3-*c*]pyridin-5-ylmethyl ester (6e): Yield 88%, mp: 154–156 °C; ^{1}H NMR, δ, ppm: 1.00 (t, $J = 8$ Hz, 3H, CH_2CH_3), 2.33 (q, $J = 9$ Hz, 2H, CH_2CH_3), 2.60 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.49 (s, 2H, $-CH_2-$), 7.13 (d, $J = 9.1$ Hz, 2H, H-2′,6′), 8.00 (d, $J = 9.8$ Hz, 2H, H-3′,5′), 8.50 (s, 1H, H-6), 9.02 (s, 1H, H-4). Anal. Calcd. for $C_{22}H_{19}N_3O_6$: C, 62.70; H, 4.54; N, 9.97. Found: C, 62.70; H, 4.51; N, 10.00.

Butyric acid 8-methyl-2-oxo-3-{3-(4-methoxyphenyl)-[1,2,4]oxadiazol-5-yl}-2*H*-pyrano[2,3-*c*]pyridin-5-ylmethyl ester (6f): Yield 87%, mp: 160 °C; ^{1}H NMR, δ, ppm: 0.91 (t, $J = 7.8$ Hz, 3H, $CH_2CH_2CH_3$), 1.52 (qv, $J = 8.7$ Hz, 2H, $CH_2CH_2CH_3$), 2.31 (t, $J = 8.7$ Hz, 2H, $CH_2CH_2CH_3$), 2.60 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.49 (s, 2H, $-CH_2-$), 7.10 (d, $J = 10.2$ Hz, 2H, H-2′,6′), 7.97 (d, $J = 8.7$ Hz, 2H, H-3′,5′), 8.50 (s, 1H, H-6), 9.00 (s, 1H, H-4). Anal. Calcd. for $C_{23}H_{21}N_3O_6$: C, 63.44; H, 4.86; N, 9.65. Found: C, 63.45; H, 4.87; N, 9.66.

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